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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,550	06/28/2001	Albert Collinson	BBC-083 A US	6240

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EXAMINER
WOODWARD, CHERIE MICHELLE

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,550	COLLINSON ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,11-88 and 96-104* is/are pending in the application.

4a) Of the above claim(s) *5-8,11 and 32-88* is/are withdrawn from consideration.

5)☒ Claim(s) *12-30* is/are allowed.

6)☒ Claim(s) *31 and 96-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's After-Final Response and Notice of Appeal, filed 1 August 2006, is acknowledged. Claims 4-8, 11-88, and 96-104 are pending. Claims 5-8, 11, and 32-88 are withdrawn as being drawn to non-elected inventions. Claims 4 and 12-31 have been indicated as allowable. Claims 96-104 stand rejected.

Finality Withdrawn

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Allowability Withdrawn

3. The indicated allowability of claim 31 is withdrawn in view of the art previously cited over claims 96-104. Claim 31 is a product-by-process claim. As such, the underlying product must be allowable in order for the claim to be allowable. In this case, the underlying product is rejected as being unpatentable over Luger, *et al* (of record) in view of Schmidt, *et al* (EP0218531) and Berg (US Patent 5622701). Rejections based on the newly cited references follow.

Response to Arguments

Claim Rejections Maintained - 35 USC § 103

4. The rejection of claims 96-104 under 35 USC 103(a) as being unpatentable over Luger, *et al* (of record) in view of Schmidt, *et al* (EP0218531) and Berg (US Patent 5622701) is maintained.

The claims are drawn to a dual specificity antibody, or antigen-binding portion thereof, that specifically binds interleukin-1α and interleukin-1β, wherein said dual-specificity antibody, or antigen-binding portion is capable of binding an antigen comprising the amino acid sequence of SEQ ID NO. 3. The claimed invention is further drawn to the dual specificity antibody, or antigen-binding portion thereof, that is fully human; chimeric; CDR grafted; humanized; comprising mouse variable region and human constant region amino sequences; comprising human heavy and light chain variable sequences containing one or more mouse CDRs; or comprising mouse heavy and light chain variable sequences containing one or more human CDRs capable of binding SEQ ID NO. 3.

Applicant argues that the Examiner has not set forth a prima facie case of obviousness. FurtherApplicant argues that there is no reason to believe that antibodies to the peptide disclosed by

Schmid et al., will bind the antigen of SEQ ID NO: 3, as disclosed by Applicant. Applicant argues that the Examiner has engaged in hindsight reasoning in constructing the obviousness rejection. Applicant's arguments filed 1 August 2006 have been fully considered but they are not persuasive.

As stated in the Office Action of 1 February 2005, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a dual specificity antibody with enhanced sensitivity against both IL-1α and IL-1β. Such antibodies would be able to neutralize IL-1 mediated inflammation more completely than an antibody directed against either cytokine, alone.

Luger, *et al* taught a dual specific antibody to IL-1α and IL-1β which recognizes a common epitope on the interleukin molecules and which may be used to develop more sensitive immunoassays for the detection of IL-1 activity in body fluids during the pathogenesis of inflammatory diseases. Schmidt et al., taught the sequence of a peptide derived from IL-1β (TKGGQDITDFT) with four common amino acids shared between IL-1α and IL-1β (ITDF). The ten amino acid sequence peptide of Schmidt et al., combined with the sequence overlap with the four amino acids that are potential antigenic epitopes of both IL-1α and IL-1β is sufficient to permit antibodies raised against the peptide of Schmidt et al., to be used to bind both IL-1α and IL-1β. For example, see, Harlow et al., Eds. Antibodies, A Laboratory Manual, 1988 Cold Spring Harbor Lab. p. 42, Table 4.1. Harlow et al., teach that small synthetic peptides with six amino acid residues in length will consistently elicit antibodies that bind to the original peptide (p. 76, first paragraph under "Size of the Peptide"). Harlow et al., also state that antibodies against smaller peptides have been reported, but generally, peptides of approximately 10 residues should be used (p. 76, first paragraph under "Size of the Peptide"). As such, it is with an understanding of the well-known teachings of Harlow et al., that the Examiner made the instant rejection under 103(a). The use of synthetic peptides as immunogens has been well known in the art since 1938 (Harlow et al., p. 72, second paragraph).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have then added the modifications of Berg in order to humanize the antibody and make it more useful for *in vivo* applications. The person of ordinary skill in the art at the time the invention was made would have been motivated to do so because an antibody with dual specificity to IL-1α and IL-1β would be able to neutralize IL-1 mediated inflammation, particularly T-helper cell activation (see, i.e. Harlow et al., Eds. *supra*, p. 42, Table 4.1), more completely than an antibody directed against either cytokine, alone.

Absent evidence to the contrary, the state of the art teaches that antibodies raised according to the teachings of Luger et al., against the peptide of Schmidt et al., which can be humanized by the modifications of Berg, will in fact bind both IL-1α and IL-1β.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

New Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Luger, *et al* (of record) in view of Schmidt, *et al* (EP0218531) and Berg (US Patent 5622701) (all previously cited in the Office Action of 1 February 2006).

The claim recites a dual-specificity antibody or antigen-binding portion thereof, that specifically binds IL-1α and IL-1β, said dual-specificity antibody, or antigen binding portion thereof obtainable by the method of claim 4. This is a product by process claim.

A product defined by the process by which it can be made is still a product claim (In re Bridgeford, 357 F.2d 679, 149 USPQ 55 (CCPA 1966)). Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

Luger, *et al* teach a dual specific antibody to IL-1α and IL-1β which recognizes a common epitope on the interleukin molecules and which may be used to develop more sensitive immunoassays for the detection of IL-1 activity in body fluids during the pathogenesis of inflammatory diseases. The relevant antigenic sequence shared by both IL-1α and IL-1β is TKGGQDITDFT. Luger, *et al* do not teach SEQ ID NO: 3.

Schmidt, *et al* teach production of antibodies against immunogenic peptides of human IL-1 (pg 2, lines 30-45). Because the immunogenic peptides disclosed by Schmidt, *et al* comprise 10 consecutive amino acids of and thus share a common epitope with the antigen of instant SEQ ID NO: 3, the antibodies disclosed by Schmidt would be capable of binding the antigen of instant SEQ ID NO: 3 (A_Geneseq_21 Database, Jan 6, 2006, Result 4, AC No. AAP71394).

Berg teaches dual specificity antibodies, which are humanized or human antibodies. Berg teaches that the humanized light chain can comprise CDRs having amino acids sequences from the light chain of a mouse antibody, and having a variable region framework sequence substantially identical to a human light chain variable region framework sequence. Berg teaches that humanized heavy chain can comprise three CDRs having amino acid sequences from the corresponding mouse antibody heavy chain with a variable region framework identical to a human heavy chain variable region framework sequence (col 3, lines 36-51). In addition, Berg teaches humanized immunoglobulins have variable region framework residues from a human immunoglobulin and CDR from a mouse immunoglobulin (col 4, lines 37-42). Berg teaches that humanized imunoglobulins have variable region framework and CDRs from a mouse immunoglobulin (col 10, lines 37-41) and that the heavy and light chain variable region framework residues can be derived from the same or different human antibody sequences (col 10, lines 49-54). Berg also teaches that human antibodies can be produced from non-human transgenic mammals having transgenes encoding at least a segment of the human Ig locus (col 12, lines 6-9). In addition, Berg teaches that bispecific (dual specific) or bifunctional antibodies have one binding site that binds to one moiety and a second binding site that specifically binds to a second moiety, which results in the ability to bind at least two different epitopes simultaneously (col 13, lines 9-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a dual specificity antibody with enhanced sensitivity against both interleukin-1α and interleukin-1β, as taught by Lugar, and to have used the immunogenic peptides taught by Schmidt to be suitable for raising antibodies against IL-1. One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have added the modifications of Berg in order to humanize the antibody and make it more useful for *in vivo* applications. The person of ordinary skill in the art at the time the invention was made would have been motivated to do so because an antibody with dual specificity to IL-1α and IL-1β would be able to neutralize IL-1 mediated inflammation, particularly T-helper cell activation (see, for example, Harlow et al., Eds. *supra*, p. 42, Table 4.1), more completely than an antibody directed against either cytokine, alone.

Absent evidence to the contrary, the state of the art teaches that antibodies raised according to the teachings of Luger et al., against the peptide of Schmidt et al., which can be humanized by the modifications of Berg, will in fact bind both IL-1α and IL-1β, rendering the instant product obvious.

Conclusion

Claims 4 and 12-30 are allowable.

Claims 31 and 96-104 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CMW

Marianne P. Allen 8/16/06

MARIANNE P. ALLEN
PRIMARY EXAMINER

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